Washington University in St. Louis
SCHOOL OF MEDICINE

Friday, October 21, 2005

RE: Comments on the reconstructed replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments.

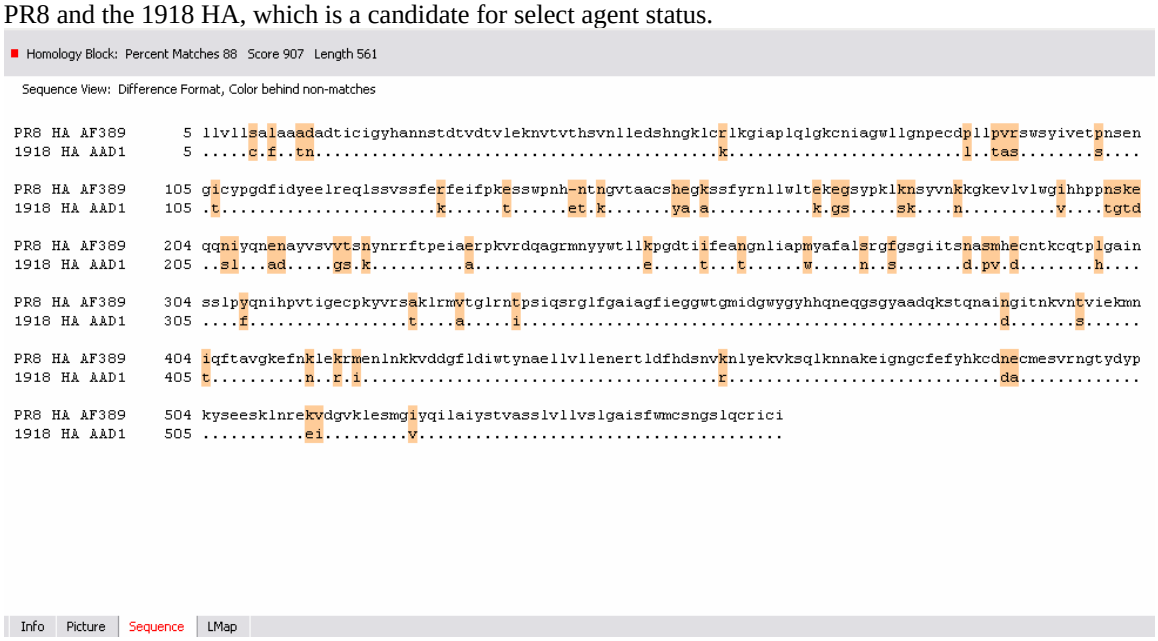
To Whom It May Concern:

I would like to comment on the interim guidelines on reconstruction of the 1918 pandemic influenza virus. As an individual interested in studying the replication and pathogenesis of influenza A virus, I am quite concerned about some of the wording in the guidelines and the implications of the guidelines for influenza virus basic and applied research.

First, the phrase "**replication competent forms of the 1918 pandemic influenza virus containing any portion of the coding regions of all eight gene segments"** seems unclear to me. Does this mean that viruses containing a portion of any one gene segment can be rescued without a select agent license but if portions of all eight gene segments are present than the virus is a select agent? Alternatively, does this mean that any coding region of any 1918 gene segment is considered a select agent? If the latter statement is true, than changing the wording from "all eight gene segments" to "any eight gene segments" might be more accurate.

Second, the vagueness of the statements strikes me as being very problematic. In figure 1, I have aligned the HA amino acid sequence of a standard laboratory strain of influenza virus, PR8, with the HA amino acid sequence of the 1918 pandemic influenza. The highlighted areas represent divergent amino acids, while the sequence that is not highlighted represents conserved amino acids. Clearly there are long stretches of amino acids that are identical between the two strains. Does this mean that a virus containing the PR8 HA gene is considered to have part of the 1918 HA gene in it? This would not be an unreasonable statement because of the high degree of identity between these proteins. If I alter the sequence of an H3 virus to that of PR8 H1, will I be guilty of introducing 1918 HA sequences into an H3 if the PR8 sequence corresponds to the 1918 virus?

Figure 1. Alignment of PR8 HA and 1918 HA amino acid sequences. The highlighted residues indicate divergent amino acids. Notice the high degree of sequence conservation between the standard lab strain PR8 and the 1918 HA, which is a candidate for select agent status.



In closing, let me clearly state that I am very much in support of measures to control the generation of recombinant viruses containing 1918 sequences. I also believe that high containment measures should be implemented when working with these viruses. However, I believe that the current wording of the rule is vague and perhaps too broad and this has the potential of negatively affecting basic and applied research on many different strains of influenza virus.

Please feel free to contact me with any additional comments or questions you may have.

Best regards,

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